Immune-evasive human islet-like organoids ameliorate diabetes.

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Authors: Eiji Yoshihara, Carolyn O'Connor, Emanuel Gasser, Zong Wei, Tae Gyu Oh, Tiffany W Tseng, Dan Wang, Fritz Cayabyab, Yang Dai, Ruth T Yu, Christopher Liddle, Annette R Atkins, Michael Downes, Ronald M Evans

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Public Summary:

Scientific Abstract:
Islets derived from stem cells hold promise as a therapy for insulin-dependent diabetes, but there remain challenges towards achieving this goal(1-6). Here we generate human islet-like organoids (HILOs) from induced pluripotent stem cells and show that non-canonical WNT4 signalling drives the metabolic maturation necessary for robust ex vivo glucose-stimulated insulin secretion. These functionally mature HILOs contain endocrine-like cell types that, upon transplantation, rapidly re-establish glucose homeostasis in diabetic NOD/SCID mice. Overexpression of the immune checkpoint protein programmed death-ligand 1 (PD-L1) protected HILO xenografts such that they were able to restore glucose homeostasis in immune-competent diabetic mice for 50 days. Furthermore, ex vivo stimulation with interferon-gamma induced endogenous PD-L1 expression and restricted T cell activation and graft rejection. The generation of glucose-responsive islet-like organoids that are able to avoid immune detection provides a promising alternative to cadaveric and device-dependent therapies in the treatment of diabetes.